September 17, 1973

Dr. Peter B. Hutt
General Counsel
Food, Drugs, and Product Safety Division
Department of Health, Education and Welfare
Rockville, Maryland 20852

Dear Peter,

The further review of cyclamate safety may give us a remarkable opportunity to apply some rational analysis to the evaluation of a food additive. There is a good deal of motivation, from different angles, to get at the root of the problem and therefore a basis for making substantial research investments. And at least as my own subjective judgment, the burden of proof is this time properly located.

In view of the problems of extrapolating from findings on animals to man I hope that something less than 100% of the effort is centered on purely empirical studies on the carcinogenicity of cyclamate in animals. Better than for most comparable situations we have a theoretical rationale for the possible biological side-effects, namely the splitting of cyclamate to cyclohexylamine and the further metabolism of this to hydroxyl derivatives which are almost certainly the actual culprits. These metabolic conversions may well not occur in the same degree in relatively short-term experiments in animals compared to chronic life-time exposure of humans. This is a matter of particular concern because of the likelihood that adapted bacterial flora, occurring rather variably in the intestinal contents of different individuals, may be responsible for the first step.

It would therefore seem reasonable forme that the problem be factored into the following components: 1) carcinogenicity of cyclohexylamine and of its hydroxylated derivatives in animals, on a quantitative basis. Since the compounds are biologically active, with much higher probability and extent than the original cyclamate, it should be much easier to collect statistically useful data; 2) it may be unethical to do further experiments with cyclamate in man and the historical data are probably sufficient. However, if there are still populations still using cyclamate they should be scrutinized further for the distribution of the capability of splitting this into cyclohexylamine; 3) if in a variety of animals one could calibrate the relative carcinogenicity of cyclohexylamine and beta-naphthylamine, we might have a resonable basis to extrapolate the risks assertained in animals to man.

In any event, given the certain knowledge that cyclohexylamine is produced in at least some human consumers as a result of the ingestion of cyclamate, it would seem reasonable to require that cyclohexylamine itself be exonerated before the parent compound can be registered. Whatever complaint there might be about the fussiness of a procedure that requires studies on metabolites as well as the original compound, ought to be dissipated by the prima facie case that already exists for the cyclohexylamine.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr

P.S. I realize most people have already made up their minds on this subject. However, I have the possibly vain hope that if Abbott would to study cyclohexylamine and verify its carcinogenicity they might even convince themselves about the hazard implicit in the product.

Perhaps I have not been following the literature sufficiently closely but I do not know of comparable biochemical information on saccharine that would be helpful in guessing at the proximal chemical hazard, if any.